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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/945,731	11/10/97	CROS	P WPB-40330

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EXAMINER	
SANDALS,W	
ART UNIT	**PAPER NUMBER**
1636	10

DATE MAILED: 11/10/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Advisory Action

Application No.	Applicant(s)
08/945,731	os, Elaissari, Mabilat, Pichot, Rodrigue And Santo
Examiner	**Group Art Unit**
WILLIAM SANDALS	1636

THE PERIOD FOR RESPONSE: [check only a) or b)]

a) ___ expires _____ months from the mailing date of the final rejection.

b) X expires either three months from the mailing date of the final rejection, or on the mailing date of this Advisory Action, whichever is later. In no event, however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

X Appellant's Brief is due two months from the date of the Notice of Appeal filed on *Oct 8, 1999* (or within any period for response set forth above, whichever is later). See 37 CFR 1.191(d) and 37 CFR 1.192(a).

Applicant's response to the final rejection, filed on *Oct 8, 1999* has been considered with the following effect, but is NOT deemed to place the application in condition for allowance:

The proposed amendment(s):

will be entered upon filing of a Notice of Appeal and an Appeal Brief.

will not be entered because:

___ they raise new issues that would require further consideration and/or search. (See note below).

___ they raise the issue of new matter. (See note below).

___ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

___ they present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: _____

___ Applicant's response has overcome the following rejection(s):

_____

Newly proposed or amended claims _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claims.

The affidavit, exhibit or request for reconsideration has been considered but does NOT place the application in condition for allowance because:

_____

The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

X For purposes of Appeal, the status of the claims is as follows (see attached written explanation, if any):

Claims allowed: _____

Claims objected to: _____

Claims rejected: *1-22*

The proposed drawing correction filed on _____ has ___ has not been approved by the Examiner.

Note the attached Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

X Other *Please see the attached response to the request for reconsideration after final rejection.*

George C. Elliott

George C. Elliott, Ph.D
Supervisory Patent Examiner
Technology Center 1600

DETAILED ACTION

Response to Arguments

1. Applicant's arguments filed on October 8, 1999 in Paper No. 9, regarding the rejection of claims 1-22 under 35 USC 103 have been fully considered but they are not persuasive. The rebuttal to the arguments is included in the repeated rejection below:

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Itoh et al. (A3), Kausch et al. (B1), Kawaguchi et al. (B2) and Hoffman et al. (B3).

The claims are drawn to a process for the isolation of nucleic material in an aqueous phase by adsorption of the nucleic material on a solid acrylamide polymer which is made from a first monomer and a second monomer which is a copolymer which has been functionalized to adsorb the nucleic material at either a pH of 7 or less, an ionic strength buffer of less than 10^{-2} M, or a temperature less than the LCST of the polymer. After the adsorption step there is step to desorb the nucleic material by increasing the ionic strength of the buffer to greater than 10^{-2},

where the pH may be increased to greater than 7, or the temperature may be increased to be greater than the LCST of the polymer. The discontinuous phase (the solid acrylamide polymer) may be separated from the aqueous phase, and the separation may be done by filtration, centrifugation, sedimentation, precipitation or the application of a magnetic field. The solid acrylamide polymer may be coated onto a non-adsorbing core which may be polystyrene, or may comprise a magnetic compound. The copolymer may comprise a nucleic acid fragment which may be a primer or probe, which may hybridize, under suitable conditions, to the nucleic material. Various acrylamide monomers for making the polyacrylamide are claimed, and as well, various cross-linking agents are claimed.

Itoh et al. taught (see especially pages 16, 18, 21, 24, 27, 44-45, 47-50 and claim 13) a process for the isolation of nucleic material in an aqueous phase by adsorption of the nucleic material on a solid acrylamide polymer which is made from a first monomer and a second monomer which is a copolymer which has been functionalized to adsorb the nucleic material at either a pH of 7 or less, or a temperature less than the LCST of the polymer. After the adsorption step there is step to desorb the nucleic material by increasing the pH, or the temperature may be increased to be greater than the LCST of the polymer. The copolymer may comprise a nucleic acid fragment which may be a primer or probe, which may hybridize, under suitable conditions, to the nucleic material. Various acrylamide monomers for making the polyacrylamide are claimed, and as well, various cross-linking agents are claimed. Itoh et al. taught the use of the method with the copolymer being an affinity ligand.

While Itoh et al. did not specifically teach the use of a low ionic strength binding buffer nor the increased ionic strength of an eluting buffer, one of ordinary skill in the art would know that the use of an affinity matrix would require the use of elements such as a low ionic strength binding buffer and an increased ionic strength buffer to elute the bound nucleic material.

Itoh et al. did not teach the discontinuous phase (the solid acrylamide polymer) may be separated from the aqueous phase, and the separation may be done by filtration, centrifugation, sedimentation, precipitation or the application of a magnetic field, nor where the solid acrylamide polymer may be coated onto a non-adsorbing core which may be polystyrene, or may comprise a magnetic compound.

a) Applicants have argued that Itoh et al. taught at pages 44-45, the "release of valuable substances" from the polymer at low temperatures and retention of the "valuable substances" at high temperatures which is contrasted to the instant claimed invention which releases "valuable substances" at high temperatures and retains "valuable substances" at low temperatures.

A further reading of Itoh et al. at page 47, lines 6-24 reveals a teaching of the general mechanism of action of the polymer. Stating that high molecular weight substances are retained at low temperatures and released at high temperatures. While Itoh et al. did not contemplate nucleic acids to be treated in this manner, it is clear that an understanding of the general

mechanism of action of the polymer is sufficient to teach one of skill in the art how to use the polymer.

The general mechanism of action of the polymer being: At temperatures below the critical solution temperature of the polymer (LCST), the pores of the polymer are open and "valuable substances" may be trapped in the interior of the pores of the polymer, and at a temperatures above the critical solution temperature of the polymer (UCST), the pores of the polymer shrink, expelling small molecular weight "valuable substances" within the pores as the polymer shrinks, and entrapping "valuable substances" which are too large to escape the pores as they shrink, or where the "valuable substances" are bound to the interstices of the pores. Hence, the general teachings of Itoh et al. are sufficient to teach one of skill in the art how to use the polymer to either entrap or expel a "valuable substance" in the pores of the polymer as the temperature of the solution rises above the critical solution temperature of the polymer.

Hoffman et al. taught (see especially the Summary of the invention and column 9, line 15 bridging to column 10, line 51) the use of an acrylamide polymer such as NIPAM, which was copolymerized with monomers which bound nucleic acids and proteins where the moiety of interest was adsorbed at an temperature below the LCST of the polymer and then desorbed at a temperature above the LCST. Hoffman et al. also taught the adsorption of a desired moiety onto the polymer with a low ionic strength or pH buffer and the desorption of the desired moiety with a high ionic strength or pH buffer.

b) Applicants have conceded that Hoffman et al. taught the release of "valuable substances" from the polymer by increasing the temperature of the solution or by increasing the ionic strength of the solution. However, applicants have argued that Hoffman et al. and Itoh et al. are not combinable because Itoh et al. did not teach that a "valuable substance" may be released by increasing the temperature of the polymer.

Since Itoh et al. did in fact teach the release of a "valuable substance" from the polymer as the temperature of the solution rises (see above), this argument is not found convincing.

Kawaguchi et al. taught (see especially columns 3-8) an acrylamide polymer coated onto beads which were bound to DNA which were used to bind proteins at a low ionic strength and elute the proteins at a high ionic strength, where the beads did not non-specifically adsorb proteins. The beads were isolated by centrifugation or filtration.

Kausch et al. taught (see especially the abstract and columns 3-10) an acrylamide polymer coated onto beads which comprised a magnetic compound. The acrylamide polymer coated beads were used to reversibly bind DNA using probes. The binding reaction took place in low ionic strength buffer and the release was effected with high ionic strength buffer. The magnetic compound in the acrylamide coated beads allowed the isolation of the bound material by a magnetic field.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to combine the teachings of Itoh et al., Hoffman et al., Kawaguchi et al. and Kausch et al. to produce the instant invention because Itoh et al., Hoffman et al., Kawaguchi et al. and

Kausch et al. were all using acrylamide polymers with a copolymer which would adsorb and desorb nucleic acids and proteins. Itoh et al. taught the use of the acrylamide polymer in bead form, and coated onto solid supports. Hoffman et al. taught the adsorption of nucleic acid in a low ionic strength buffer and the desorption of the nucleic acid in a high ionic strength buffer. Kawaguchi et al. and Kausch et al. taught the coating of polyacrylamide onto solid bead supports, and Kausch et al. taught the polyacrylamide coated beads which comprised a magnetic compound to facilitate the isolation of the bead with the bound DNA in a magnetic field.

One of ordinary skill in the art would have been motivated at the time of the instant invention to combine the teachings of Itoh et al., Hoffman et al., Kawaguchi et al. and Kausch et al. to produce the instant invention because Itoh et al., Hoffman et al., Kawaguchi et al. and Kausch et al. taught the desirable use of acrylamide polymers with a copolymer which would adsorb and desorb nucleic acids and proteins. Itoh et al. taught the use of the acrylamide polymer in bead form, and coated onto solid supports. Hoffman et al. taught the desirable method of adsorption onto an acrylamide solid support of nucleic acid in a low ionic strength buffer and the desorption of the nucleic acid in a high ionic strength buffer. Kawaguchi et al. and Kausch et al. taught the coating of polyacrylamide onto solid bead supports, and Kausch et al. taught the polyacrylamide coated beads which comprised a magnetic compound to facilitate the isolation of the bead with the bound DNA in a magnetic field. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in producing the instant claimed invention given the teachings of Itoh et al., Hoffman et al., Kawaguchi et al. and Kausch et al.

Response to Arguments in Paper No. 9

4. Applicants have asserted that Itoh et al. did not teach a cross-linked polymer of cationic monomers. Itoh et al. at page 24, lines 11-21, taught the use of cationic monomers in the cross-linked polymers.

5. Applicants have argued that Itoh et al. does not teach **specific** (emphasis added) examples of binding nucleic acids to a copolymer. This is acknowledged in the above rejection. However, it is also noted in the above rejection that Itoh et al. taught the use of the copolymer to bind high molecular weight molecules such as nucleic acids.

6. Applicants have argued that Itoh et al. taught at page 45, lines 11-13, that "[t]hese compounds may be held at high temperatures and released at low temperatures." This section of Itoh et al. is discussing the entrapment of high molecular weight molecules by the shrinking and swelling of the pores of the gel, and does not refer to the adsorption of molecules to the gel by ionic or electrostatic forces which are promoted by pH or the ionic strength of the buffer, and as such does not apply to the claimed invention of base claims 1 and 3.

7. Applicants have argued that Itoh et al. does not teach the use of pH at most equal to 7, nor an ionic strength at most equal to 10^{-2} M. Itoh et al. did teach the use of acidic pH's (ie. less than 7) at page 48, line 25 bridging to page 49, line 9, and lines 18-19. At page 50, lines 4-11, Itoh et al. discusses the use of ionic monomer with either anionic or cationic properties for the purpose of binding moieties by ionic interaction. Itoh et al. does not discuss the ionic strength of the buffer. Hoffman et al. taught the use of 0.1M buffer and water in Figure 6, as exemplary high

ionic strength buffers and low ionic strength buffers, demonstrating the change in elution times of methylene blue by displacement in high and low ionic strength buffers.

8. Kausch et al. and Kawaguchi et al. are relied upon to demonstrate the application of coating a solid support with the copolymer for the purposes of selective binding of large molecules such as nucleic acids, which is discussed in Itoh et al. at page 17, line 19 bridging to page 20, line 4.

Conclusion

9. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner
November 8, 1999

George C. Elliott, Ph.D
Supervisory Patent Examiner
Technology Center 1600